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TITLE: A Placebo-Controlled Trial of Prazosin vs. Paroxetine in Combat Stress-Induced PTSD Nightmares and Sleep Disturbance

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14. ABSTRACT The primary goal of this proposal is to evaluate the efficacy and tolerability of the alpha-1 adrenergic antagonist prazosin compared to placebo for combat trauma-related nightmares, sleep disturbance and overall function in recently combat-exposed returnees from OIF and OEF. A secondary goal is to evaluate the effects of the SSRI paroxetine on behavioral symptoms and overall function in this population. Specific hypotheses (described below) will be tested in a three parallel arm 12-week randomized controlled trial of prazosin, paroxetine and placebo in combat-exposed troops recently returned from OIF and OEF with combat trauma-related persistent nightmares and sleep disturbance. This will be a two-site study performed in the Seattle/Tacoma area at Madigan AMC and in the Washington DC area at Walter Reed AMC.					
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Introduction

The primary goal of this proposal has been to evaluate the efficacy and tolerability of the alpha-1 adrenergic antagonist prazosin compared to placebo for combat trauma-related nightmares, sleep disturbance, and overall function in recently combat-exposed returnees from OIF and OEF. A secondary goal has been to evaluate the effects of the SSRI paroxetine on behavioral symptoms and overall function in this population. We attempted to achieve these goals in a three parallel arm 12-week randomized controlled trial of prazosin, paroxetine and placebo in combat-exposed troops recently returned from OIF and OEF with combat trauma-related persistent nightmares and sleep disturbance. This two-site study was performed in the Seattle/Tacoma area at Madigan AMC and in the Washington DC area at Walter Reed AMC.

Body

IRB approvals - All study procedures and the consent forms were approved by both the IRBs of Madigan Army Medical Center (AMC) and Walter Reed AMC. The current approval period for Madigan is 6/27/08-6/19/09. The current approval period for Walter Reed is 1/9/08-1/10/09.

Hiring/training of study personnel - all study personnel at VA Puget Sound Health Care System for performing all clinical study tasks at Madigan AMC and coordination, data management, and statistical analysis for both Madigan AMC and Walter Reed AMC were hired and training and certification for staff performing study activities at Madigan AMC was completed June 1, 2006. Hiring of personnel at the Walter Reed AMC site was completed. The Seattle team conducted a study initiation visit at Walter Reed AMC in 11/06; final training and certification of staff at WRAMC was completed February 1, 2007. The following personnel received pay from this research effort: Andrew David, Dan Gonzalez, Sarith Keo, Steve Millard, Dan Morelli, Denise Pritzl, Anita Ranta, Kasse Rupp, Vincent Wu, and Carol Xiang.

Recruitment and enrollment of study subjects

Subject enrollment into the three-arm study has been:

Madigan AMC

- 189 subjects telephone prescreened
- 98 subjects consented
- 76 subjects randomized to treatment
- 22 study completers

Walter Reed AMC

- 108 subjects referred
- 72 subjects telephone prescreened
- 13 subjects consented
- 9 subjects randomized to treatment
- 6 study completers

It became clear that retention remained inadequate in the three-arm protocol to achieve meaningful results. Therefore, we modified the design to a prazosin vs. placebo augmentation trial to salvage our primary goal – determining efficacy of prazosin for combat trauma nightmares in this population. We also have taken an aggressive approach to recruitment and retention by meeting with and explaining the importance and value of the prazosin study to the leadership of combat units at Madigan AMC. Investigators Murray Raskind, MD and Lt. Col. Kris Peterson, MD, have met with commands of the 4th Stryker Brigade, 2nd ID (Col. John Norris, CSM Jeff Huggins), the 42nd MP Brigade (Col. Lois Beard, Lt. Col. Gillian Boise), the Warrior Transition Battalion (Lt. Col. John Bolton, FSG Creed McCaslin), and the Family Readiness Group (Ms. Regina Toomey) that provides support to these units. These educational and

information exchange meetings have resulted in firm commitments of enthusiastic support for the study and numerous referrals from each unit. This groundwork has facilitated improved recruitment and (most critically) retention in the trial.

Completion of clinical trial procedures – Screening and baseline assessments, repeat assessments and follow-up, and completion of case report forms are ongoing under the new augmentation trial design through a subsequent grant.

Data monitoring and database management – Construction of the database was completed August 1, 2006. Data entry and data cleaning are continuous through a subsequent grant.

Statistical analysis and preparation of manuscripts and reports – pending study completion.

Key Research Accomplishments – This is the first placebo-controlled trial of a behaviorally active drug in an active duty military population ever attempted. We have overcome substantial obstacles and are now on the way to completing the study successfully through a subsequent grant.

Research Findings – A manuscript describing the unique challenges of conducting a psychotropic drug trial in an active duty population is in preparation.

Conclusions – The efficacy of prazosin for combat trauma nightmares and sleep disruption already demonstrated in Vietnam War veterans remains under investigation by our group in OIF/OEF returnees.

References – none.

Appendices – none.